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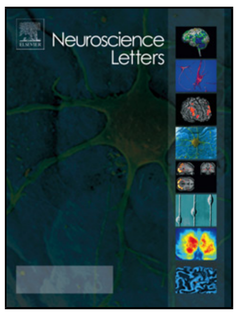

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Global field synchronization of 40Hz auditory steady-state response: does it change with attentional demands?

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Highlights

- A net-effect of attentional demands on auditory steady-state response was studied
- Auditory stimulation at 40 Hz results in global synchronization
- Stronger synchronization occurs during stimuli counting and resting with closed eyes
- Synchronization during distracting task is lower independently of stimulation

Abstract

Auditory steady-state responses (ASSRs) are increasingly used in research of neuropsychiatric disorders and for brain-computer interface applications. However, results on attentional modulation of ASSRs are inconclusive. The evaluation of large-scale effects of task-related modulation on ASSRs might give better estimation of the induced changes.

The aim of the study was to test global field synchronization - a reference-independent evaluation of the amount of phase-locking among all active regions at a given frequency – during tasks differing in attentional demands to 40 Hz auditory stimulation. Twenty seven healthy young males participated in the EEG study with concurrent 40 Hz binaural click stimulation and three experimental tasks: 1) to count presented stimuli (focused attention); 2) to silently read a text (distraction); 3) to stay awake with closed eyes (resting). We showed that during auditory 40 Hz stimulation, the global field synchronization of the EEG increased as compared to the silent baseline period and the largest increase was observed when subjects counted stimuli or rested with closed eyes. Our results provide insights that depending on the method of assessment, the 40 Hz ASSR might be an indicator of both local and complex synchronization processes that are affected by the state (task performed or psychopathology) of the participants.

Keywords: Auditory steady-state response; ASSR; 40Hz; Attention; Global Field Synchronization; GFS

1. Introduction

The auditory steady-state responses (ASSRs) are brain responses recorded with the electroencephalogram or magnetoencephalogram to periodically presented auditory stimuli. The response reaches the greatest magnitude with stimulation around 40 Hz (referred to as 40 Hz ASSR) [1]. The ASSRs are used to index the brain's ability to generate synchronous responses in neuropsychiatric disorders [2–4] and are increasingly used in various brain-computer interface applications [5,6]. Both areas of application imply that ASSRs are sensitive to the factors/conditions affecting the processing of auditory stimuli. For example, in clinical applications, ASSRs are thought to reflect decreased abilities to generate responses in the gamma frequency band, reflecting impairments of cognitive processing [7,8]. Similarly, in BCI applications, the changes induced by attentional modulations in ASSRs are practically used to control devices [9].

However, the existing reports on the sensitivity of ASSRs to changes in attentional level are controversial – increments of ASSRs with attention directed to the stimulation have been reported by some authors [10–14], while others reported the responses to be insensitive to attentional manipulations [15,16]. All the existing studies evaluating attentional effects on ASSRs used the amplitude/power or inter-trial phase coherence (phase-locking index, PLI); these were measured from the single EEG channel with maximal response, or from a group of channels/sensors around the area of the strongest response [10,17,18]. Among the ASSR measures, the phase-locking index is known to give the most stable results and is least affected by the noise [4,19]. The PLI allows to assess the EEG phase stability in reference to the stimulus onset and, thus, reflects the engagement of stimulation-specific (locally defined) neural populations (e.g. [20,21]). The observable changes in PLI, as induced by the varying attentional demands to stimulation, are attributed to the alterations of the activity within these local networks. Nevertheless, attentional processes per se are related to the activity within the large-scale distributed neural systems [22,23]. This suggests that evaluation of large-scale effects of task-related modulation on ASSRs might give better estimation of the induced changes.

Koenig et al. (2001) proposed a method called *global field synchronization* (GFS) that estimates the amount of phase alignment across all channels as a function of frequency [24]. This allows to evaluate the presence of networks connected through non-lagged oscillations during resting state [24] and in response to stimulation [25]. The method is reference-independent and global; it avoids the problem of repeated testing and does not require explicit source models for the interpretation of the results [24]. The GFS approach has successfully been used to estimate functional connectivity in sleep [26], to show changes in schizophrenia [24] and Alzheimer's disease [27], and to evaluate global synchrony in the gamma range during anesthesia [28]. The utility of the method as applied to ASSRs has been tested in patients with schizophrenia [22]. The approach provided clinically relevant information on impaired binding abilities [25] allowing to discriminate subjects with auditory verbal hallucinations from those who had no history of hallucinations. Importantly, the discrimination in the same sample was not possible based on the phase-locking index, i.e. assessing the synchronization precision from trial to trial [29]. This suggests that the local phase-locking of the response across trials and the global field synchronization during the stimulation may provide distinct information on the brain's ability to generate periodic responses. In addition, since GFS is sensitive to the presence of lags among neural sources, it relates to a theoretical framework of network formation that emphases the importance of nearly simultaneous oscillations across network nodes [30].

The aim of the current study was to estimate large-scale synchrony (assessed with global field synchronisation) in response to 40 Hz auditory click stimulation and to evaluate changes induced by different attentional demands to stimulation. Based on earlier studies, we expected higher global synchronization when subjects focused on the auditory stimulation and lower global synchronization when subejcts were distracted from the stimulation. Additionally, we evaluated GFS during resting with closed eyes, as this condition was used in the original work by Koenig et al (2012) [25] and the largest ASSRs in this condition were previously shown by Griskova-Bulanova et al. (2011) [31].

2. Methods

Subjects

Twenty seven healthy non-smoking right-handed males (to exclude potential influence of hormonal fluctuations [32]) participated in the study (mean age 23.2, SD 2.4). Subjects were asked not to smoke and consume caffeine-containing drinks at least one hour prior to the experiment. The hearing thresholds of all subjects were within the norm range (<25dB HL at octave frequencies). The study was approved by the Lithuanian Bioethics Committee and all participants gave their written informed consent.

Stimulation

The forty hertz click stimulation trials lasted 500ms and consisted of 20 identical bursts of white noise (1.5 ms) in duration. The overall settings were similar to those previously used [31]. The auditory stimuli were designed in Matlab (The Math-Works, Inc.). The experiment was programmed and presented using Psychopy software [33]. The inter-stimulus interval was set at 700-1000 ms. The sounds were presented binaurally through Sennheiser HD 280 PRO earphones; sound pressure level was adjusted to 60dBA with a DVM 401 decibel meter (Velleman, USA). A Cedrus StimTracker (Cedrus Corporation, San Pedro, CA) was used to ensure a minimal delay between the presentation of the stimulus to the participant and the marking of stimulus onset in the data.

Attentional modulation

The experiment was designed to induce an attentional modulation of the ASSRs similarly to previous studies [17,34]. While subjects were comfortably seated in an electrically and sound-shielded recording chamber, they were asked to perform three experimental tasks: 1) to count presented stimuli while fixating a cross and report the number of stimuli presented (further referred as counting); 2) to silently read an easily readable and catching text that was presented on the computer screen and to ignore the sounds; this was followed by a brief report on the content of the reading material (further referred as reading) and 3) to stay awake with closed eyes and to let their thoughts wander and not to focus on stimulation (further referred as closed eyes/EC). The order of tasks was randomized across the participants. Stimuli were presented 120 times during each run.

EEG recording

EEG was recorded using an ANT device (ANT Neuro, The Netherlands) and a 64 channel WaveGuard EEG cap. Mastoids were used as a reference. Impedance was kept below 20 kΩ and the sampling rate was set at 1024 Hz. Vertical and horizontal electro-occulograms (VEOG and HEOG) were recorded from above and below the left eye and from right and left outer canthi.

EEG processing

The off-line processing of EEG data was performed in EEGLAB for MatLab© [35,36]. The power-line noise was removed using multi-tapering and Thomas F-statistics implemented in CleanLine plugin for EEGLAB. Channels with substantial noise throughout the recording were rejected. An independent component analysis (ICA) was performed on the remaining channels with the ICA-implementation of EEGLAB ('runica' with default settings) and independent components related to eye blinks and lateral eye movements were removed. Epochs of 1500 ms were created starting at 500 ms prior to the stimulus onset and lasting for 1000 ms post-stimulus onset; the epochs were further inspected for remaining artifacts. The removed channels were reconstructed using spherical spline method [37]. The final number of trial included into further analyses was 115.22 ± 6.11 for counting; 114.48 ± 5.56 for reading , and 115.31 ± 7.04 for EC.

Data analysis

For the global field synchronization (GFS) analysis, a custom-written script was used. The data was transformed into the frequency domain using wavelet transformation (a complex Morlet wavelet, constant number of wavelet cycles = 7) for every time-frequency point within 30-50 Hz within a -500 to 1000 ms time window. This yielded sine and cosine values for each time-frequency point and electrode. The distribution of sine-cosine points, thus, is indicative of the amount of phase synchronization across channels. The distribution was submitted to a two-dimensional principal component analysis (PCA). The ratio of the first and the second PCA components (GFS) described the shape of the sine-cosine points (reflecting the predominant phase angle) [24]. The GFS was calculated as [24]:

$$GFS(f,t) = \frac{|E(f,t)_1 - E(f,t)_2|}{E(f,t)_1 - E(f,t)_2}$$

where $E(f,t)_1$ and $E(f,t)_2$ are the eigenvalues 1 and 2 obtained from the PCA at frequency f and time point t. More details on the approach can be found at [24,26].

Mean GFS values were extracted focusing on the 38-42 Hz frequency window for the silent baseline (-400 to 0 ms) and stimulation period (100-500 ms, corresponding to the late-latency gamma response, where ASSR is not contaminated by the onset response [29,38,39]). GFS reactivity was calculated as a difference of mean GFS values per frequency during the stimulation period (100 to 500 ms) against the mean baseline period GFS value per frequency during the baseline (-400 to 0 ms) [25]. These data were subjected to statistical evaluation, performed in STATISTICA, version 10 (Stat Soft, Inc., 2011). Data were normally distributed as indicated by Shapiro-Wilk tests. The repeated measures ANOVA (rmANOVA) with factors TIME (silent baseline vs stimulation) and TASK (closed eyes vs reading vs counting) was performed on the means of GFS values. Also a separate rmANOVA to evaluate the effect of TASK (closed eyes vs reading vs counting) on the GFS reactivity was conducted. Subsequent post-hoc testing with Bonferroni correction was applied and adjusted p-values are reported.

3. Results

An increase of global field synchronization during the stimulation period occurred at around 40 Hz as expected (Figure 1A). The maximal global synchronization was reached within the time window of 200-350 ms as can be seen from Figure 1C, representing the reactivity plots of GFS in all three experimental conditions. This corresponded well with previous findings using the inter-trial phase coherence measure [40,41]. For visualization, time-frequency plots were calculated as the averages of all subjects: GFS values at each frequency point were corrected to the corresponding baseline activity (-400 to 0 ms), resulting in the grand averaged time-frequency plots for GFS reactivity. Means and standard deviations of GFS values at the baseline and during the stimulation in all three experimental tasks are presented in Table 1.

GFS values during the silent baseline were compared to GFS values during auditory 40 Hz stimulation in all three tasks. The effect of TASK (closed eyes vs reading vs counting) was not significant: $F_{2,52}$=0.834, p = 0.44, partial $\eta^2 = 0.03$. Higher GFS values were obtained during stimulation than at the baseline in all three tasks – the rmANOVA indicated a significant effect of TIME (baseline vs stimulation; $F_{1,26}$=19.007, p < 0.001, partial $\eta^2 = 0.42$). A significant interaction between TIME and TASK factors ($F_{2,52}$=7.940, p < 0.001, partial $\eta^2 = 0.23$) was observed. Post-hoc comparisons revealed that at the baseline and during the stimulation lower GFS estimates were observed during reading (distraction from stimulation) than during closed eyes (p = 0.02 at the baseline and p < 0.001 during the 40 Hz stimulation) and while counting (p = 0.01 at the baseline and p < 0.001 during the 40 Hz stimulation). Means and 0.95 confidence intervals of the GFS at the baseline and during stimulation in all three conditions are depicted in Figure 1B.

A significant effect of TASK was revealed for the GFS reactivity estimates, measured as the difference between stimulation and baseline ($F_{2,52}$=7.940, p < 0.001, partial $\eta^2 = 0.23$) and showing a capability to synchronize with the stimulation. Post-hoc comparison indicated significantly larger stimulation-baseline difference in the closed eyes condition as compared to reading (p < 0.001); no difference between the closed eyes condition and the counting condition was observed (p = 0.17) and reactivity during counting did not differ from that during reading (p = 0.14).

4. Discussion

We aimed to evaluate the effect of varying attentional demands on the global-scale synchronization of EEG in response to 40 Hz auditory stimulation in a group of healthy young male subjects. Our results suggest that with auditory stimulation at 40 Hz, global field synchronization increases: the GFS values during auditory stimulation were higher than during the silent baseline period. The largest GFS estimates were observed when direct attention was paid to the stimulation (stimuli were counted) and when subjects rested with closed eyes and let their thoughts wander. Importantly, the reading task that distracted from the stimulation did not prevent a net increase in synchronization to occur (Figure 1C). Nevertheless, brain synchronization during an engaging reading task was lower both during the silent baseline and during auditory stimulation as compared to counting and resting tasks. The lowest reactivity (GFS changes from the baseline) to the auditory stimulation was also observed during distraction.

Forty Hz ASSRs are increasingly used in neuropsychiatric populations: some authors argue that these responses reflect the integrity of auditory circuits [8,20,42,43], while others interpret ASSRs in terms of global synchronization of neural activity with the external environment [2,25,38]. For the evaluation of the net synchrony/connectivity of electroencephalographic responses, various methods can be employed [44]. However only the coherence between brain areas following 40 Hz periodic auditory stimulation was used before: Mulert et al. (2011) applied the coherence as a connectivity measure in patients with schizophrenia and Yamasaki et al. (2005) employed the coherence measure in healthy controls to assess the rapid temporal processing in the auditory cortex [45,46].

From the methodological point of view both the GFS and coherence measure connectivity and report connectivity values between 0 (no evidence of connection or synchrony) to 1 (perfect connection or synchrony). However, the assumptions behind the measures are very different. High coherence value suggests that two electric signals are related but these signals might or might not be separated in time [47]; contrarily, GFS assesses how well the signals are aligned in time across all channels. Additionally, coherence considers connectivity between pre-selected spatial locations, allowing evaluation of separate neural networks: for example, Yamasaki et al. [45] reported significantly higher coherence of C1–C2 and C3–C4 pairs than for any other combination of electrodes. GFS, on the contrary, does not require prior knowledge on the active brain areas and it is assumed that activity of each neural network may be reflected in all electrodes [26]. Due to the global nature, GFS is a reference free measurement [27], whereas coherence is dependent on the reference settings [48]. The abovementioned features make GFS a useful measure for global synchronization assessment with multichannel EEG recordings that might be used for the estimation of modulatory roles of various factors/conditions /tasks on both resting-state and stimulation-related processes.

Koenig et al. (2012) were the first to apply GFS approach to ASSRs: in their study using auditory 40 Hz stimulation, a marginal trend was observed for global synchronization to occur in healthy subjects (p=0.08) when they were resting with closed eyes. Our results provide evidence that with the periodic stimulation at 40 Hz, global synchronization changes occur as reflected by higher GFS values during the stimulation when compared to the baseline. This is in line with findings by Yamasaki et al. (2005), reporting higher coherence values during stimulation as compared to silence. Functionally, the increase of EEG synchronization at the stimulation frequency points to the synchronized activation among the network loops representing the stimulus; this is achieved by the functional integration of network elements through phase-locked oscillations [25,45].The difference in the results of Koenig et al.

(2012) and the current study could be attributed to two methodological differences between the studies. First, we investigated the process in a uniform young sample of healthy males in contrast to Koenig et al. (2012), where subjects served as controls for schizophrenia patients (24-55 years range) and were matched on age and gender to the patient group. Secondly, we applied a wavelet transform instead of the FFT that allowed us to track temporal aspects of the response.

Based on the existing literature, we expected differences in synchronization level between a focused-on-the-stimulus task (counting) and a distraction task (reading): many authors using click stimulation reported increase of locally assessed response amplitude and phase-locking while direct attention was paid to the stimulation [10,49]. We observed the expected focused attention-distraction difference in the global synchronization level measured with GFS. Moreover, with the same experimental settings, we were able to show phase-locking and amplitude differences between distraction and focused conditions in our previous study [34]. However, our GFS results also showed that the level of synchronization per se (regardless the presence of auditory stimulation) is sensitive to the task being performed – during the engaging reading, the level of synchronization was lower than during unfocused attention with closed eyes and focused attention on the auditory stimulation while counting stimuli. The gamma ‘deactivation’ was previously observed during high-order processing of complex visual objects [50] and during reading [51–53]; moreover, it was proposed to be global [54]. As pointed out by Koenig et al. (2012), GFS can be treated as a measure of the global synchronicity that is mediated by a network of cortico-cortical connections and is suited to study a hypothesized general functional binding between extended neural networks. Thus, our observation of lower GFS during distraction from auditory stimulation is compatible with our earlier interpretation of lower phase-locking index and evoked power measures as a result of sensory cortical inhibition of task-unrelated sensory information [31]. This interpretation is based on the assumption that a strong attentional focus required by demanding visual tasks (like reading) does not allow subjects to process the irrelevant auditory input equally [55], presumably being more inhibitory when the distracting task is more engaging as the 40 Hz ASSRs are sensitive to the concurring task load [18]. However, this assumption should be investigated further. Overall, our observation fits within the recently proposed model, suggesting that the entrainment of neuronal oscillations might function as a global mechanism used by the brain to optimize attention and stimulus perception [56].

We suggest that the GFS measure allows the evaluation of a general state of the networks involved in the processing of auditory periodic stimuli. Importantly, the reactivity – a GFS change during auditory stimulation from the silent baseline - was substantially higher in the closed eyes condition as compared to the reading (but not counting) and no differences were found between the reading and counting tasks. This would imply that in the closed eyes condition, the brains of young males are more susceptible to synchronization with the periodic auditory stimulation. This finding is congruent with our previous studies showing that phase-locking is higher in closed eyes condition as compared to distraction and comparable to focused attention condition [31,34,57]. Alternatively, effects of involuntary shifts of attention during the closed eyes condition could have occurred and influenced the results; however, this is unlikely as we did not find any difference between the reactivity in the distracting condition and focused attention condition where the level of focused attention to stimulation was different.

5. Conclusions

We showed that 1) during auditory 40 Hz stimulation, the global field synchronization of the EEG increased as compared to the silent baseline period and 2) the largest increase was observed when subjects rested with closed eyes or were counting stimuli. Our results provide insights that depending on the method of assessment, the 40 Hz ASSR might be an indicator of both local and complex synchronization processes that are affected by the state (task performed or psychopathology) of the participants.

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The Authors declare that there is no conflict of interest.

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Legends

Figure 1. (A) The plot of GFS reactivity values at each frequency point (30-50 Hz window, 1 Hz step) for three experimental conditions; (B) Means and 0.95 confidence intervals of the mean GFS at the baseline and during the stimulation in three experimental conditions, *p<0.05, **p<0.001; (C) Time-frequency plots of GFS reactivity in three experimental conditions.

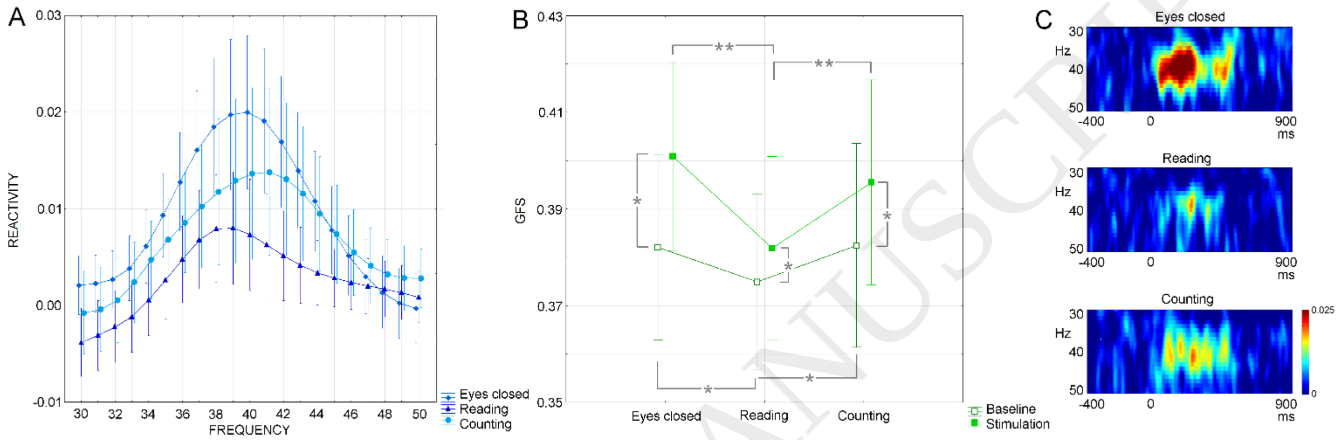

Table 1. Means and standard deviations of GFS values during the baseline and during the 40 Hz stimulation for three experimental conditions.

GROUP	CLOSED EYES		READING		COUNTING	
	Baseline	Stimulation	Baseline	Stimulation	Baseline	Stimulation
MEAN	0.382	0.401	0.375	0.382	0.382	0.396
SD	0.048	0.048	0.045	0.047	0.052	0.053